Relationship between alveolar functional fraction and clinical outcomes in children during postoperative care after surgery for single-ventricular heart

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ABSTRACT

Background : **Optimization of pulmonary to systemic blood flow (Qp:Qs) is the key to postoperative care of children with a single-ventricular heart. The ratio of end-tidal CO2 to partial pressure of CO2 called alveolar functional fraction (AFF) has shown a strong relationship with Qp:Qs in the catheterization lab in this population (with Qp:Qs of 1 correlating with AFF of 0.7). As there are no studies to understand the relationship between AFF and clinical outcomes in the postoperative care of these children, this study was carried out.**

Methodology and Results : **This retrospective cohort study included 29 postoperative periods of children who underwent surgery for a single-ventricular heart. The average AFF was calculated for each early postoperative period. The primary clinical outcome was time in hours to normalize lactate. Other clinical outcomes included duration of mechanical ventilation, duration of milrinone infusion; presence of acute kidney injury (AKI), seizures and necrotizing enterocolitis (NEC); need for tracheostomy, need for extra-corporeal support, and mortality in the first 60 days postoperatively. The study population was divided into Group 1 with AFF ≤0.7 and Group 2 with AFF >0.7, to compare the outcome differences between the groups. Time to normalize the lactate had a modest negative correlation with the AFF, with Pearson's $r = -0.49$ ($P = 0.007$) for the entire cohort. The clinical outcomes were not statistically different for groups with AFF ≤0.7 and with AFF >0.7, although the group with AFF ≤0.7 had a higher incidence of NEC and higher mortality, whereas the group with AFF >0.7 had a higher incidence of AKI.**

Conclusions : **In this small study, the AFF showed a modest negative correlation with the time to normalize lactate in postoperative care after surgery for a single-ventricle heart. There were the trends with some other important clinical outcomes but not statistically significant. A larger, multi-center study is needed to delineate these relationships further.**

Keywords : Alveolar functional fraction, end-tidal CO2, pulmonary to systemic blood flow, single ventricular heart

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INTRODUCTION

The overall objective of surgical intervention in single ventricular heart is to allow the functioning ventricle (whether morphologically right or left) to supply the systemic circulation and to connect the systemic veins directly to the pulmonary artery (PA). This procedure cannot be done in the neonate since PA pressure and resistance are high. Consequently, it is performed as staged procedures.[1] With improvement in surgical techniques and postoperative care, these diagnoses have significantly improved outcomes, with interstage mortality decreasing to <10% in many centers.[2]

However, the early postoperative period after initial surgery for a single-ventricular heart still remains one with high risk due to inherent inefficiencies of parallel circulation and the inferior power source of the postischemic single ventricle.[3] For example, the mortality after the initial surgery for hypoplastic left heart syndrome (HLHS) is estimated to be 12%, most commonly due to cardiovascular causes.[4] The pulmonary vascular resistance can change, sometimes widely, and the pulmonary to systemic blood flow (Qp:Qs) ratio will also vary, despite adequate management. Imbalances of Qp:Qs and limited myocardial reserve of the morphological right ventricle (RV) compounded with inadequate systemic oxygen delivery and end-organ perfusion account for most of the early mortality.[5] Mixed venous saturation (SvO_2) along with systemic oxygen saturation is used to estimate Qp:Qs during postoperative care.[3,6] The bedside estimation of Qp:Qs from SaO_2 alone has been advocated on the basis of untested assumptions: constant systemic arterio-venous oxygenation difference and normal pulmonary venous saturations ($SpvO_2$) of ≥95%. However, there is variability in both SvO_2 and $SpvO_2$ after the Stage-1 procedure, making SpO_2 a poor predictor of Qp:Qs.[7]

Recently, a novel bedside parameter calculated based on end-tidal CO_2 ($EtCO_2$) termed alveolar functional fraction (AFF) – a ratio of $EtCO_2$ to partial pressure of CO2 in arterial gas (PaCO2) has been shown to have strong linear relationship with Qp:Qs during cardiac catheterization in children with single-ventricular heart physiology, with AFF of approximately 0.7 correlating with Qp:Qs of 1 in this population.[8] The AFF can be easily calculated at the bedside during the immediate postoperative period with arterial blood gas (ABG) as $EtCO_2$ is continuously monitored when the patient is invasively ventilated. Being a novel clinical parameter, there are no data on the relationship between AFF and clinical outcomes in children undergoing initial surgery for single ventricular heart.

METHODOLOGY

This retrospective cohort study was performed at the pediatric cardiac center of a free-standing tertiary care children's hospital. The data were collected by reviewing individual charts from the electronic medical record (EMR). The study was approved by the institutional review board. As the study was retrospective, the need for informed consent was waived.

Data collection

We included postoperative periods of patients who had undergone initial surgical interventions for single ventricular heart in the 1st month of life. Other inclusion criteria were (1) presence of arterial line and multiple ABG analysis available (2) mechanical ventilatory support and $EtCO_2$ data available postoperatively to allow for calculation of two separate values of AFF at least 12 h apart. We had to exclude patients if they were (1) in early extubation or death with the inability to get 2 separate readings about 12 h apart (2) came out from the operative room on extracorporeal life support (3) If AFF >1 as it was likely an error of calibration. As $EtCO_2$ was not reported in the EMR before October 2015, we could not include any prior patients.

Data collected for each postoperative period were demographics including (1) age (in days) at the time of procedure, (2) sex, (3) weight in kg, and (4) height in cm. Clinical data collection included (1) congenital heart disease diagnosis and (2) operative procedure performed. The AFF ($EtCO_2$:$PaCO_2$) was calculated after postoperative arrival to the intensive care unit with the initial blood gas and subsequently for up to 4 separate blood gases approximately at 12 h if available. Average AFF was assigned only if two separate values were available postoperatively separated by 12 h, this average AFF was defined as primary exposure.

The clinical outcome data were collected for those with assigned average AFF. The primary outcome was time to normalize lactate to <2 mmol/L in h. The secondary outcomes included (1) duration of mechanical ventilation in hours, (2) duration of milrinone in hours, (3) Development of acute kidney injury (AKI) with elevated creatinine of >0.3 and/or urine output <0.5 mL/kg/h with documentation of a diagnosis of AKI, (4) Use of continuous renal replacement therapy (CRRT) or hemodialysis, (5) Clinical documentation of a diagnosis of necrotizing enterocolitis (NEC), (6) Diagnosis of sepsis or septic shock, (7) placement of tracheostomy, (8) Diagnosis of seizures, (9) extracorporeal life support provision with extracorporeal membrane oxygen (ECMO) any time after first 12 h of coming out of the operative room, and (10) mortality.

The entire study group was divided into two subgroups based on AFF to study the relationship between AFF and clinical outcomes. Postoperative periods with AFF ≤0.7 were labeled as Group 1, likely to have Qp:Qs ≤1. Those with AFF >0.7 were labeled as Group 2, likely to have Qp:Qs >1. The clinical outcomes were compared between both groups.

Statistical analysis

A Pearson's correlation coefficient was calculated between AFF and the primary outcome of time to lactate normalization in hours for the entire cohort. Similarly, a Pearson's correlation coefficient was calculated between AFF and secondary outcomes with continuous variables including duration of mechanical ventilation hours and duration of milrinone support in hours. Subsequently, demographic and clinical outcomes were compared between subgroups 1 and 2. A Student's *t*-test was performed for normally distributed data and the Mann–Whitney *U*-test was performed if the data were not normally distributed. A Fisher's exact test was performed to compare the ratio categories for Group 1 and Group 2.

RESULTS

Out of 48 postoperative period patients, three were excluded from the analysis as they required ECMO support immediately after the operative room, 13 were excluded as there were no adequate data on $EtCO_2$ or blood gas analysis in EMR to obtain at least 2 ratios, and 3 were excluded due to early extubation or death. The remaining 29 postoperative periods underwent data collection and analysis. The most common diagnosis was HLHS for 15 of these postoperative periods. Other diagnoses were atrioventricular canal defect with unbalanced ventricle with small left ventricles (LVs), single ventricle with mitral atresia (corrected transposition with right-sided atrioventricular valve atresia), pulmonary atresia with intact ventricular septum, truncus arteriosus with interrupted aortic arch (IAA), critical aortic stenosis, aortic arch hypoplasia, single ventricle with double-inlet LV with subaortic RV, heterotaxy with single ventricle, and IAA with ventricular septal defect. Six of the patients had undergone a hybrid approach which included branch PA bands with stent placement in ductus arteriosus followed by another surgery of RV to PA conduit placement. Both of those postoperative periods were counted as separate incidences.

As shown in Table 1, there was almost a 1:1 ratio of males to females overall, and the mean AFF was 0.737:1. The most common postoperative cardiac diagnosis was a hypoplastic left heart with RV-PA conduit ($n = 8$). The average age for the first intervention was 10.3 days, with an average weight of 3.25 kg.

Figure 1 demonstrates Pearson's correlation between the AFF and various individual outcomes including the primary outcome of time to lactate resolution and other outcomes such as length of mechanical ventilation and duration of vasopressor use and a comparison of time to lactate resolution between Group 1 and Group 2. Time to lactate resolution had a moderate negative correlation with the AFF, with Pearson's $r = -0.49$ and $P = 0.007$. Duration of mechanical ventilation and duration of vasopressor use did not have a significant correlation with the AFF.

Table 1: Summary of patient's baseline demographic information, including gender, age, weight, height, the alveolar functional fraction, and cardiac diagnosis with intervention

Demographic data	Overall (*n*=23)
Gender, *n* (%)	
Female	11 (47.8)
Male	12 (52.2)
Age at the time of surgery (days)	
Mean (SD)	10.3 (11.4)
Median (minimum–maximum)	7.00 (1.00–44.0)
Weight (kg)	
Mean (SD)	3.25 (0.507)
Median (minimum–maximum)	3.20 (2.32–4.06)
Height (cm)	
Mean (SD)	48.5 (4.36)
Median (minimum–maximum)	48.0 (33.5–55.5)
$EtCO_2$:$PaCO_2$ ratio	
Mean (SD)	0.737 (0.159)
Median (minimum–maximum)	0.740 (0.380–1.07)
Diagnosis	
HLHS with RV-PA conduit	8
HLHS with BT shunt	15

SD: Standard deviation, HLHS: Hypoplastic left heart syndrome, $EtCO_2$: End-tidal CO_2, $PaCO_2$: Partial pressure of CO_2, RV-PA: Right ventricle-pulmonary artery, BT: Blalock taussing

Table 2 shows the comparison of clinical outcomes of ventilator days, duration of vasopressor use, and time to lactate resolution between Group 1 and Group 2. The *P* values are calculated from the Mann–Whitney *U*-test comparing the median between the two categories since ventilator days, duration of vasopressor use, and time to lactate resolution are not normally distributed. There is no significant difference between ratio categories in terms of ventilator days, duration of vasopressor use, and time to lactate resolution.

Table 3 shows a summary of various outcomes stratified between Group 1 and Group 2. The *P* values are calculated from the Fisher's exact test to see if outcomes of interest are related to the ratio categories since the counts are small. The outcomes were not significantly different between the groups.

Table 4 shows a summary of the AFF by different outcome status. The *P* values are calculated from a *t*-test to compare the average AFF for AKI, NEC, Neuro, ECMO, and mortality. Mann–Whitney *U*-test is used to compare the median ratio between yes/no groups for infection. The *P* values indicate that there is no big difference in the $EtCO_2$:$PaCO_2$ ratios (AFF) between yes/no groups in each factor.

DISCUSSION

This study is the first to evaluate the relationship between a novel but easily calculated bedside clinical parameter named the AFF as a surrogate for Qp:Qs and clinical outcomes. We studied this relationship in the immediate postoperative period after initial surgery for a single ventricular heart when fluctuation of the Qp:Qs is expected.

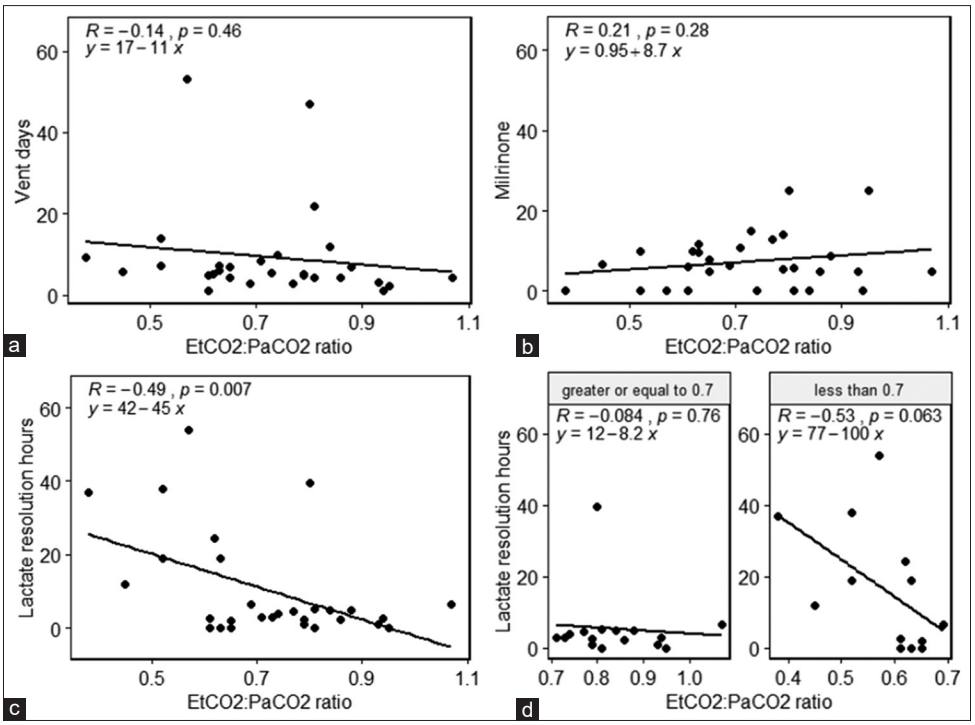

Figure 1: Correlation plots between end-tidal CO_2 ($EtCO_2$):$PaCO_2$ ratio (alveolar functional fraction) and length of mechanical ventilation (a), duration of vasopressor use (b), and time to lactate resolution (c). Correlation plots between $EtCO_2$:$PaCO_2$ ratio and time to lactate resolution between Group 1 and Group 2 (d). $EtCO_2$: End-tidal CO_2

Table 2: Summary of ventilator days, milrinone, and lactate resolution time for groups with alveolar functional fraction ≤0.7 (Group 1) or alveolar functional fraction >0.7 (Group 2)

	Overall (*n*=29)	Group 1 (*n*=13)	Group (*n*=16)	*P*
Ventilator days				
Mean (SD)	9.40 (12.0)	9.86 (13.3)	9.02 (11.3)	0.54
Median (minimum–maximum)	5.50 (1.00–53.0)	6.00 (1.10–53.0)	5.15 (1.00–47.0)	
Milrinone				
Mean (SD)	7.26 (6.73)	5.60 (4.29)	8.61 (8.10)	0.56
Median (minimum–Maximum)	6.00 (0.00–25.0)	6.30 (0.00–11.6)	5.70 (0.00–25.0)	
Lactate resolution (h)				
Mean (SD)	10.3 (14.5)	16.5 (17.6)	5.31 (9.34)	0.19
Median (minimum–Maximum)	4.00 (0.00–54.0)	12.0 (0.00–54.0)	3.00 (0.00–39.6)	

SD: Standard deviation

We found a moderate inverse correlation between the AFF and time to normalize lactate resolution even with a small study population. The outcomes of our study indicate the need for further research in regarding this novel parameter.

Optimal Qp:Qs to improve the outcomes after the surgery for a single ventricular heart has been a point of debate for many years. Mathematical models have suggested that Qp:Qs <1 is associated with better outcomes, especially in the HLHS type of single ventricular physiology.[9,10] Clinically, Qp:Qs between 1 and 2 correlated with the best postoperative hemodynamic status and consequently better outcomes and lower mortality, in this population.[5,11] The calculations for bedside Qp:Qs estimation are based on the assumption of $SpvO_2$ being ≥97%. Pulmonary venous desaturation due to pulmonary disease, ventilation-perfusion mismatch, or pulmonary arteriovenous fistulae is common during the postoperative period. This leads to inaccuracy in the oxygen-based calculation of Qp:Qs.[5,7] On the other hand, as CO_2 is more soluble and diffusible, Qp:Qs estimation based on CO_2 can be more reliable during these events of pulmonary venous desaturations. In a recent study performed on children with single ventricular physiology undergoing cardiac catheterization, the AFF (a CO_2-based calculation) was found to have a very strong relationship with Qp:Qs, with Qp:Qs of 1 correlating approximately to AFF between 0.7 and 0.8.[8] The study was based on a single value of AFF and Qp:Qs calculated during cardiac catheterization for these patients. The patients were in a steady state and it did not provide data on any clinical outcomes.

In previous studies comparing the clinical outcomes during postoperative care of these children, using bedside Qp:Qs using oxygen-derived indices has found a good correlation between Qp:Qs and clinical outcomes such as lactate clearance, vasoactive medication use, oxygen

Table 3: Clinical outcomes comparison between the groups

	Overall (*n*=29), *n* (%)	Group 1 (*n*=13), *n* (%)	Group 2 (*n*=16), *n* (%)	*P*
AKI				0.44
No	19 (65.5)	10 (76.9)	9 (56.2)	
Yes	10 (34.5)	3 (23.1)	7 (43.8)	
CRRT				-
No	29 (100)	13 (100)	16 (100)	
Yes	0	0	0	
NEC				0.36
No	23 (79.3)	9 (69.2)	14 (87.5)	
Yes	6 (20.7)	4 (30.8)	2 (12.5)	
Infection				0.19
No	27 (93.1)	11 (84.6)	16 (100)	
Yes	2 (6.9)	2 (15.4)	0	
Trach				-
No	29 (100)	13 (100)	16 (100)	
Yes	0	0	0	
Neuro				1
No	24 (82.8)	11 (84.6)	13 (81.2)	
Yes	5 (17.2)	2 (15.4)	3 (18.8)	
ECMO				1
No	25 (86.2)	11 (84.6)	14 (87.5)	
Yes	4 (13.8)	2 (15.4)	2 (12.5)	
Mortality				0.30
No	25 (86.2)	10 (76.9)	15 (93.8)	
Yes	4 (13.8)	3 (23.1)	1 (6.2)	

ECMO: Extracorporeal membrane oxygen, NEC: Necrotizing enterocolitis, CRRT: Continuous renal replacement therapy, AKI: Acute kidney injury

Table 4: Summary of alveolar functional fraction by different factor status

	Overall (*n*=29), *n* (%)	AFF, mean (SD)	AFF, median (range)	*P*
AKI				
No	19 (65.5)	0.73 (0.16)	0.69 (0.45–1.07)	0.61
Yes	10 (34.5)	0.70 (0.17)	0.74 (0.38–0.93)	
CRRT				
No	29 (100)	0.72 (0.16)	0.73 (0.38–1.07)	-
Yes		-	-	
NEC				
No	23 (79.3)	0.73 (0.16)	0.74 (0.38–1.07)	0.80
Yes	6 (20.7)	0.71 (0.16)	0.64 (0.52–0.95)	
Infection				
No	27 (93.1)	0.73 (0.16)	0.74 (0.38–1.07)	0.30
Yes	2 (6.9)	0.63 (0.01)	0.63 (0.62–0.63)	
Trach				
No	29 (100)	0.72 (0.16)	0.73 (0.38–1.07)	-
Yes	0	-	-	
Neuro				
No	24 (82.8)	0.72 (0.16)	0.73 (0.38–1.07)	0.98
Yes	5 (17.2)	0.73 (0.15)	0.73 (0.52–0.93)	
ECMO				
No	25 (86.2)	0.74 (0.15)	0.73 (0.45–1.07)	0.35
Yes	4 (13.8)	0.62 (0.21)	0.66 (0.38–0.80)	
Mortality				
No	25 (86.2)	0.75 (0.14)	0.74 (0.52–1.07)	0.10
Yes	4 (13.8)	0.54 (0.18)	0.49 (0.38–0.80)	

ECMO: Extracorporeal membrane oxygen, NEC: Necrotizing enterocolitis, CRRT: Continuous renal replacement therapy, AKI: Acute kidney injury, AFF: Alveolar functional fraction, SD: Standard deviation

saturations, and mortality.[5,12] It has been also seen that minimum blood lactate level within the first 24 h after the Sano-Norwood procedure is a highly discriminatory predictor of perioperative mortality.[12,13] Photiadis *et al.* showed that optimal hemodynamic status, end-organ function, and higher survival correlates with Qp:Qs between 1 and 2, although maximum oxygen delivery was likely below Qp:Qs below 1.[5] Our study, even with a small sample sized showed a moderate negative correlation between AFF (our Qp:Qs surrogate) and time to normalize lactate. This association is significant as lactate clearance is an important factor affecting morbidity and mortality after surgical palliation with single-ventricular physiology. Our study, by showing the relationship between the AFF and the lactate clearance, complements both of the above studies.

The $EtCO_2$ monitoring is routinely done along with invasive mechanical ventilation in most intensive care units, including early postoperative care of children undergoing palliative surgery for single ventricular physiology.[14] These children also undergo frequent ABG analysis providing multiple $PaCO_2$ values during their early postoperative care.[15] Thus, with each ABG analysis, the AFF is easily calculated as a ratio of $EtCO_2$ to $PaCO_2$ at the bedside providing an estimation of Qp:Qs. In fact, pairing with the EMR, automatic calculation, and flagging for the staff of overly permissive pulmonary blood flow at the expense of systemic blood flow can easily be achieved.

We studied multiple other clinical outcomes such as duration of milrinone use, duration of mechanical ventilation, AKI, CRRT, ECMO support need, and mortality; we did not find any statistical difference between our study groups of AFF ≤0.7 and AFF >0.7. Earlier studies have indicated that Qp:Qs <1 is associated with decreased urine output, higher lactate levels, higher vasopressor use, and mortality. AFF being a surrogate for Qp:Qs may show some more meaningful associations if studied on a larger scale.

As $EtCO_2$ is a product of $PaCO_2$, its value cannot be greater than $PaCO_2$, and as a result, the AFF cannot be >1. If $EtCO_2$ is higher than $PaCO_2$, it is likely a calibration error, and the AFF is not reliable under those circumstances. In patients with excess pulmonary blood flow or a Qp:Qs >1, the gap between $PaCO_2$ and $EtCO_2$ will decrease bringing the AFF ratio closer to 1, but not exceeding it. Considering physiological dead space ventilation of 10%, any value of the AFF >0.9 can be considered unreliable, especially in the setting of suspected increased blood flow. A change in the AFF can alert bedside providers of changes in Qp:Qs but other measures to estimate Qp:Qs are needed under such circumstances. The AFF can also fluctuate in a postoperative patient due to pulmonary disease, atelectasis, and hypovolemia. These confounders need to be taken into consideration while interpreting the relationship between the AFF and Qp:Qs. With this limitation, the AFF can only be used as an additional tool along with other parameters to predict Qp:Qs such as routine Qp:Qs estimation based on oximetry, cerebral near infrared spectrometry, lactate value, or hemodynamic monitoring. It will not be useful as a single tool to predict Qp:Qs.

Due to the retrospective nature of the study, we were not able to ensure frequent timely ABG collection and as a result adequate number of AFF values for patients. This resulted in a very limited number of patient enrollments. Our study parameter – the AFF is based on the $EtCO_2$, which is only available in case of invasively mechanical ventilation. Our inclusion criteria also warranted an average of at least two values of the AFF calculated 12 h apart so any early extubation meant we were not able to enroll those patients. With this limitation to ensure an adequate sample size, we needed to include patients with single-ventricular hearts with different physiology than classic HLHS. The inclusion of these patients means that the interpretation of the results of this study will have limitations in validity and applicability.

Limitation of the study

One of the important limitations of the study is the retrospective design and small sample size. The retrospective design also meant we were only able to describe the association between the AFF and clinical outcomes. The small sample size meant we were not able to find statistically significant associations. The confounding factors (pulmonary disease, atelectasis, and hypovolemia) were not able to be accounted for due to the retrospective study design with a small sample size. A larger, multi-center, and prospective study can further explore these relationships.

CONCLUSIONS

We studied a novel parameter named the AFF ($EtCO_2$:$PaCO_2$ ratio), which can be easily derived at the bedside, as a surrogate for Qp:Qs to assess its relationships to clinical outcomes in postoperative care after initial surgeries for the single-ventricular heart. We found that it has a moderate inverse correlation with time for lactate clearance. We also observed relationship trends with some other important clinical outcomes but having a very small study group for these rare disease groups it was difficult to establish statistical significance. A large, prospective, multicenter study will be able to assess those relationships better.

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Conflicts of interest

There are no conflicts of interest.

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